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CASE REPORT

Concurrent hypopituitarism and leukemic retinopathy in a child with B-precursor acute lymphoblastic leukemia and isolated central nervous system relapse

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ABSTRACT

Hypopituitarism in leukemia is very rare. In addition, central nervous system (CNS) relapse and leukemic retinopathy in childhood acute lymphoblastic leukemia (ALL) have declined with the use of modern systemic chemotherapy that includes CNS prophylaxis. Here, we report the case of a 4-year-old girl who received chemotherapy and intrathecal therapy without CNS radiation after a diagnosis of B-precursor ALL without CNS involvement. Three months after chemotherapy completion, she presented with lower-extremity weakness and was diagnosed with an isolated CNS relapse. Concurrent hypopituitarism and leukemic retinopathy were also found. After receiving craniospinal radiotherapy and systemic chemotherapy, her retinopathy and vision improved. She is now in complete remission, and she is still on chemotherapy according to the guideline from the Pediatric Oncology Group. Although rare, hypopituitarism and leukemic retinopathy should be taken into consideration in patients with CNS involvement by leukemia.

Key Words Hypopituitarism, retinopathy, acute lymphoblastic leukemia, central nervous system relapse

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children[1]. With advances in systemic polychemotherapy and the introduction of preventive central nervous system (CNS) therapy, the incidence of CNS relapse has declined to less than 5%–10%. Hypopituitarism has been reported as the initial presentation or relapse in acute myeloid leukemia[2,3] or as the initial presentation in chronic lymphocytic leukemia[4]. Primary lymphoma in the pituitary gland has also been noted[5]. Hypopituitarism in children with ALL appears to be quite rare, having been reported in only 1 child, and is associated with radiation[6,7]. Like CNS relapse, the incidence of leukemic retinopathy has declined with the progression of CNS-directed treatment.

Here, we report the case of a child with CNS relapse of ALL that manifested as weakness together with concurrent hypopituitarism and leukemic retinopathy. Written informed consent was obtained from the patient and her parents for publishing her individual details and any accompanying images in this manuscript.

CASE DESCRIPTION

A 4-year-old girl originally displayed symptoms of fever for 7 days. An elevated leucocyte count (28.78×10^9/L), with anemia (hemoglobin: 6.8 g/dL) and thrombocytopenia (92×10^9/L), was noted in peripheral blood. Bone marrow examination showed markedly hypercellular marrow with diffused infiltration by blasts. Flow cytometric analyses of the blasts was consistent with B-precursor ALL. The karyotype of the blast cells was 45,XX. No nucleated cells were found in the cerebrospinal fluid (CSF).

Given the diagnosis of B-precursor ALL without CNS involvement, the patient received chemotherapy according to the Taiwan Pediatric Oncology Group ALL-2002 standard-risk protocol[8] (Table I). In brief, prednisolone, vincristine, epirubicin, and L-asparaginase were used for induction, and consolidation therapy consisted of 6-mercaptopurine and 4 courses of high-dose methotrexate. Afterward, dexamethasone, vincristine, epirubicin, and L-asparaginase were used for re-induction. Maintenance chemotherapy included dexamethasone, vincristine,

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6-mercaptopurine, and methotrexate. For CNS prophylaxis, triple intrathecal chemotherapy with methotrexate, hydrocortisone, and cytarabine was administered. No prophylactic cranial irradiation was given. No lumbar puncture was traumatic. Remission was achieved at the end of induction therapy, and the patient remained in complete remission after finishing 2.5 years of chemotherapy.

Weakness of both legs, with a limping gait, were found 3 months after completion of chemotherapy. A neurologic examination demonstrated intact cranial nerves. No evidence of relapse was found in a bone marrow aspiration and biopsy, but in CSF, white cells 3.464×10^9/L, of which 95% were blasts, were found. Flow cytometric analysis of the CSF blasts showed them to be of B-precursor lineage. Magnetic resonance imaging of the spine showed an abnormal infiltrative mass with heterogeneous enhancement in the S1–2 epidural space, suggesting leukemic involvement. Isolated CNS relapse of ALL was diagnosed, and the patient received chemotherapy according to the Pediatric Oncology Group guideline[9].

At the time of CNS relapse, edema was noticed in the girl's upper and lower extremities. Investigations for an endocrine cause revealed low T3 (38.01 ng/dL; reference: 90–230 ng/dL), low total T4 (3.68 μg/dL; reference: 4.5–10.0 μg/dL), low free T4 (0.58 ng/dL; reference: 0.7–2.0 ng/dL), and low thyroid-stimulating hormone (0.27 IU/mL; reference: 0.5–4.5 IU/mL). When a single low growth hormone (GH) level of 0.065 ng/mL (reference: >7 ng/mL) after exercise was found, the patient underwent 2 separate GH provocation tests using clonidine and insulin hypoglycemia to assess GH response[10]. On both tests, all peak GH levels were found to be less than 7 ng/mL, indicating GH deficiency. Very low, and even undetectable, levels of adrenocorticotropic hormone (<5.00 pg/mL; reference: 7.2–63.3 pg/mL), low morning fasting cortisol (<0.4 μg/dL; reference: 6.7–22.6 μg/dL), and low evening cortisol (<0.4 μg/dL; reference: 2.5–12.5 μg/dL) all indicated a central origin of hypocortisolism. Serum prolactin and insulin-like growth factor 1 were within their normal ranges. Urinary specific gravity, plasma and urinary osmolarities, and urine and serum sodium levels were all within their normal ranges. Magnetic resonance imaging of brain showed thickening and increased bilateral enhancement in the hemispheric dura, indicating dural involvement of the leukemia. Additionally, a focal nodular enlargement about 7×4 mm at the left lateral aspect of pituitary gland was found (Figure 1).

After hypopituitarism was found, the patient was treated with cortisone acetate (10 mg/m^2 in divided doses twice daily) and L-thyroxine (2 μg/kg daily). No GH replacement was given because GH replacement has been reported to be associated with leukemia[11].

The patient's cortisol level returned to the normal range 2 months after initiation of treatment with cortisone acetate; replacement therapy was subsequently tapered and then discontinued. High free T4 was noted after the supplementation with L-thyroxine and that replacement therapy was also tapered and discontinued.

During the re-induction chemotherapy after CNS relapse, the patient complained of bilateral blurred vision and progressive visual loss. Her corneas were clear and the anterior chambers and vitreous were silent; however, funduscopic examination revealed severely swollen optic discs, blurred disc margins, tortuous and sheathing retinal vessels in the posterior poles radiating from disc to

TABLE I Chemotherapy protocol used

Treatment stage and drug	Dose	Schedule
Induction (5 weeks)		
Prednisolone	40 mg/m^2	Days 1–28
Vincristine	1.5 mg/m^2	Days 1, 8, 15, 22
Epirubicin	20 mg/m^2	Days 1, 8
L-Asparaginase	5000 IU/m^2	Weeks 1–3, 3 times weekly
Triple intrathecal therapy[a]		Days 1, 5
Consolidation (8 weeks)		
6-Mercaptopurine	40 mg/m^2	Days 1–56
Methotrexate	2.5 g/m^2	Days 1, 15, 29, 43
Triple intrathecal therapy[a]		Days 1, 15, 29, 43
Re-induction [3 weeks (17–19 and 27–29)]		
Dexamethasone	8 mg/m^2	Days 1–8, 15–21
Vincristine	1.5 mg/m^2	Days 1, 8, 15
Epirubicin	30 mg/m^2	Days 1.8
L-Asparaginase	5000 IU/m^2	Weeks 1–9, 3 times weekly
Triple intrathecal therapy[a]		1
Maintenance (120 weeks)		
Methotrexate	40 mg/m^2	Daily 6-mercaptopurine and weekly methotrexate
6-Mercaptopurine	60 mg/m^2	
Vincristine	2 mg/m^2	Dexamethasone plus vincristine every 4 weeks until week 100
Dexamethasone	12 mg/m^2	
Triple intrathecal therapy[a]		

[a] Methotrexate 12 mg, hydrocortisone 24 mg, and cytarabine 36 mg.

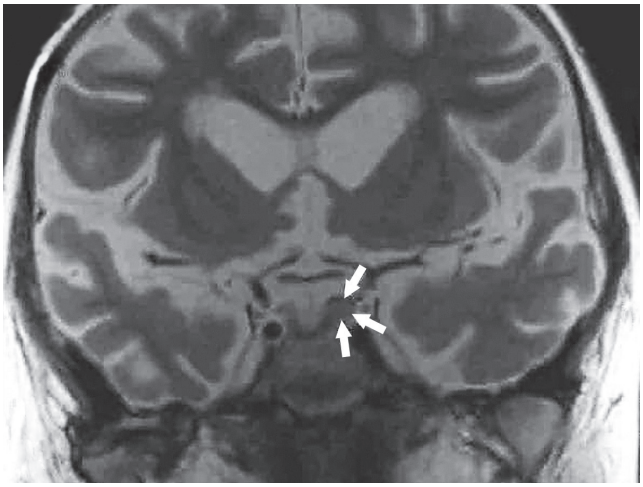

FIGURE 1 Magnetic resonance imaging of brain. A focal nodular enlargement about 7×4 mm at the left lateral aspect of pituitary gland was noted (arrows). Bilateral dilated ventricles were also found.

macula areas, and flame-shaped hemorrhage in both eyes (Figure 2). She was diagnosed with leukemic retinopathy, and craniospinal irradiation to a total dose of 24 Gy was immediately begun. At the end of radiotherapy, visual findings were all improved, but not completely resolved. At present, her CSF is negative for disease. Her weakness and vision have improved.

DISCUSSION

With advances in therapy, the cure rate in childhood ALL has reached approximately 80%–90%[1,12,13]. The CNS is the most common site of leukemic extramedullary invasion. On the basis of our Taiwan Pediatric Oncology Group ALL-2002 report, only 3.0% of children with ALL experience isolated CNS relapse[8]. In ALL, CNS relapse is reported to be associated with T-cell lineage, a high white blood cell count at diagnosis, and traumatic punctures[14,15]. Our patient had none of those risk factors, but presented with neurologic changes that signalled CNS relapse. A CNS relapse should be considered in any patient with leukemia who has neurologic symptoms or signs, even those at lower risk of CNS relapse. A CNS relapse can manifest in many ways, but the occurrence of hypopituitarism and leukemic retinopathy in our patient were unusual and are highlighted in this report.

Except for radiation-induced hypopituitarism[6], only Nishi *et al.*[7] have reported a child with hypopituitarism in ALL. Our patient was diagnosed with hypopituitarism because of her low thyroid-stimulating hormone, low GH after GH provocation tests, and low adrenocorticotropic hormone. It is interesting that the hypopituitarism required only temporary replacement therapy and resolved with craniospinal irradiation.

All ocular structures have been found to be involved in patients with CNS leukemia[16]. Overt leukemic infiltration of the eye is uncommon at presentation and is usually associated with leukemic relapse[17,18]. It suggested that, like the CNS and testes, the eye could be a sanctuary site in ALL[19]. In leukemic retinopathy, leukemic infiltrations and hemorrhage can be found in the retinal area by funduscopic examination[20]. Although the prognosis for restoration of vision is poor, visual recovery after emergent radiotherapy has been reported[21]. In our patient, unlike the patient reported by Nishi et al [7], a typical leukemic retinopathy with CNS relapse was found, together with hypopituitarism. Because visual changes might not be appreciated or expressed by young children, funduscopic examination should be routine in patients with ALL and CNS relapse.

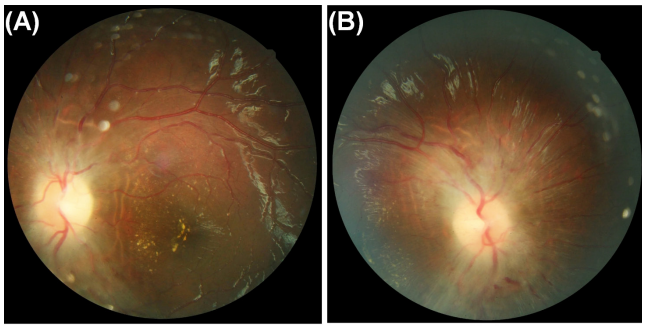

FIGURE 2 The fundi of (A) the right eye and (B) the left eye by funduscopic examination. Severely swollen optic discs, blurred margins of discs, tortuous and sheathing retinal vessels in posterior pole radiating from disc to macula area, and flame-shaped hemorrhea.

SUMMARY

A CNS relapse in childhood ALL is uncommon, but can manifest in many ways. All patients with relapse should undergo evaluation of the eyes, because visual changes might not be appreciated by young children. Endocrine dysfunction occurs only rarely with CNS relapse, but should be investigated in patients with symptoms or findings suggesting a possible endocrine origin.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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